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Craniosynostosis Suggestive of Saethre-Chotzen Syndrome: Clinical Description of a Large Kindred and Exclusion of Candidate Regions on 7p

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We decribe the clinical manifestations of an autosomal dominant form of craniosynostosis in a large family with eight affected relatives. Unilateral or bilateral coronal synostosis, low frontal hair line, strabismus, ptosis, and partial cutaneous syndactyly of fingers and toes are findings suggestive of the diagnosis of Saethre-Chotzen syndrome. The disease locus was excluded from the two adjacent Saethre-Chotzen candidate regions on 7p by linkage analysis with markers D7S664 and D7S507. This indicates heterogeneity of Saethre-Chotzen syndrome with a locus outside the candidate regions on 7p. © 1996 Wiley-Liss, Inc.

KEY WORDS: Saethre-Chotzen syndrome, craniosynostosis, linkage analysis, heterogeneity

INTRODUCTION

Craniosynostosis is defined as premature closure of one or more cranial sutures. It is a manifestation of more than 60 syndromes, which are usually autosomal dominant traits [Cohen, 1986, 1988]. A subgroup of craniosynostosis syndromes [the acrocephalosyndactyly syndromes (ACS)] is characterized by concomitant abnormalities of the distal limbs.

The causative mutations in a subset of ACS have been detected in fibroblast growth factor receptor (FGFR) genes. To date three FGFR genes have been found to be associated with craniosynostosis. Apert syndrome (ACS I) is caused by mutations within exon 7 of the FGFR2. Mutations in exon 9 of this gene cause the Jackson-Weiss syndrome, Pfeiffer syndrome (ACS IV), and Crouzon syndrome. Pfeiffer syndrome is also caused by a mutation in FGFR1 [for review, see Cohen, 1995], and recently a mutation in FGFR3 in Crouzon syndrome was observed [Meyers et al., 1995]. In Saethre-Chotzen syndrome (ACS III), considered to be the most frequent acrocephalosyndactyly syndrome, two adjacent candidate regions have been defined at 7p, between D7S664 and D7S507 [Lewanda et al., 1994], and between D7S488 and D7S654 [Rose et al., 1994; Tsuji et al., 1995].

Saethre-Chotzen syndrome is an autosomal dominant condition with high penetrance and variable expressivity. It is characterized by craniosynostosis usually involving one or both coronal sutures, and in some cases the metopic or the lambdoid suture. However, the craniosynostosis is not an obligate trait in this syndrome. A wide range of anomalies is seen in Saethre-Chotzen syndrome including facial asymmetry, a low frontal hairline, ptosis of the eyelids, deviation of the nasal septum, brachydactyly, and mild cutaneous syndactyly, most often of the second and third fingers and toes [Cohen, 1986; Pantke et al., 1975; Reardon and Winter, 1994].

Here we report on a four-generation pedigree with autosomal dominant craniosynostosis suggestive of Saethre-Chotzen syndrome. All affected members show unilateral or bilateral coronal synostosis of variable expressivity; strabismus, ptosis, or partial cutaneous syndactyly are present in some of them. A severe plagiocephaly was corrected surgically in two infants. Using linkage analysis with markers D7S664 and D7S507, the disease locus in this family was excluded from the two candidate regions at 7p. The data presented indicate heterogeneity of Saethre-Chotzen syndrome with a locus outside the known candidate regions on 7p.

SUBJECTS AND METHODS

Pedigree

An autosomal dominant form of craniosynostosis segregates in this four-generation family (Fig. 1). In par-

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

ticular we are concerned with two young patients (IV-6 and IV-8, Fig. 2) who came to surgery at the age of 7.5 years and 7 months, respectively. Consanguinity is not present in the family. Physical examinations were performed personally in 21 relatives by one investigator (S.G.). Photographs with frontal, lateral, and caudocranial view of the head and of the hands and feet were taken with each subject's consent. The photographs were reviewed independently by two craniofacial surgeons (J.F., W.M.). Radiographic studies of the skull were performed in four individuals, and radiographic analysis of the hands and feet were performed in one affected individual.

Linkage Studies

Genotyping using microsatellite markers. Microsatellite analysis was performed for loci D7S664 and D7S507. The PCR reaction mixture included 300 ng genomic DNA template;150 ng of each of the forward and reverse primer; 200 μM each of dATP, dGTP, dCTP, and dTTP; 1.5 mM $MgCl_2$; 10 mM Tris-HCl (pH 8.3); 50 mM KCl; 0.01% gelatin; 10 μCi 32P-dCTP; and 0.5 U Taq polymerase. Amplification of each 50 μl sample was performed in a thermal cycler (Perkin Elmer Cetus, Norwalk, CT) for 30 cycles, denaturation at 94°C for 1 min, annealing at 55°C for 1 min, and extension at 72°C for 1 min. These cycles were followed by a single cycle of 7 min at 72°C; 4 μl aliquots of each reaction mixture were subjected to electrophoresis in 6% polyacrylamide 8 M urea denaturing gels, dried by vacuum, and exposed to Fuji RXfilm overnight.

Linkage analysis. Linkage analysis was performed using the MLINK and LINKMAP programs of the LINKAGE program package (version 5.1.) [Lathrop and Lalouel, 1984]. ACS in this family was assumed to be an autosomal-dominant disorder. To reduce the possibility of false exclusion we performed the analysis using a penetrance of 80% in addition to 100%, although there was no evidence for non-penetrance in the family investigated. An ACS allele frequency of 1 in 10,000, a mutation rate of 1 in 100,000, and equal allele frequencies for markers were assumed. Exclusion was assumed if the lod score did not exceed -2.0 [Morton, 1955].

RESULTS

Clinical Report

Patient 1 (IV-8). The proposita (IV-8) was born as the third child of a 27-year-old mother (III-15) and a 31-year-old father (III-16) at 38 weeks gestation after an uneventful pregnancy. Birth length was 48 cm (25th–50th centile), weight was 3,380 g (75th–90th centile), and Apgar scores were 10/10 at 1 and 5 min, respectively. A facial asymmetry with deviation of the nasal septum was noted.

At age 7 months she was referred to the neurosurgical department because of marked plagiocephaly (Fig. 2). At this age, her length was 71 cm (90th centile), weight was 7.2 kg (10th–25th centile), and head circumference (OFC) was 43 cm (50th–75th centile). Clinical manifestations included plagiocephaly with a high asymmetric forehead (left side prominent), low frontal hairline, asymmetric face, strabismus, and clinodactyly of the 5th left finger (Figs. 2, 4). Physical examination did not show other abnormalities of hands and feet. Radiographic studies of the skull demonstrates premature synostosis of the right coronary suture (Fig. 2). At age 3 years her psychomotoric development is normal.

Patient 2 (IV-6). The propositus (IV-6) is the first child of the couple (III-15 and III-16). He was born at term by cesarian section, when the mother was 20 and the father was 24 years old. Birth length was 50 cm (50th–75th centile), weight was 3,250 g (50th–90th centile), and Apgar scores were 10/10. Plagiocephaly and facial asymmetry with deviation of the nasal septum were noted (Fig. 2).

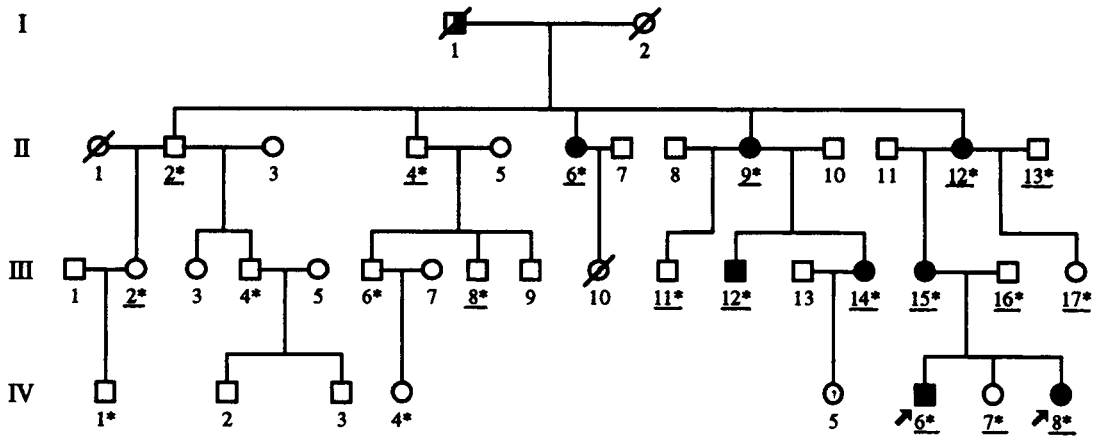

Fig. 1. Pedigree of the craniosynostosis kindred. Individuals personally investigated are indicated by an asterisk, and individuals from whom DNA was used for linkage studies are underlined. Filled symbols represent affected, open symbols unaffected, and the half-filled symbol allegedly affected individuals. III-10 and IV-5, status unknown.

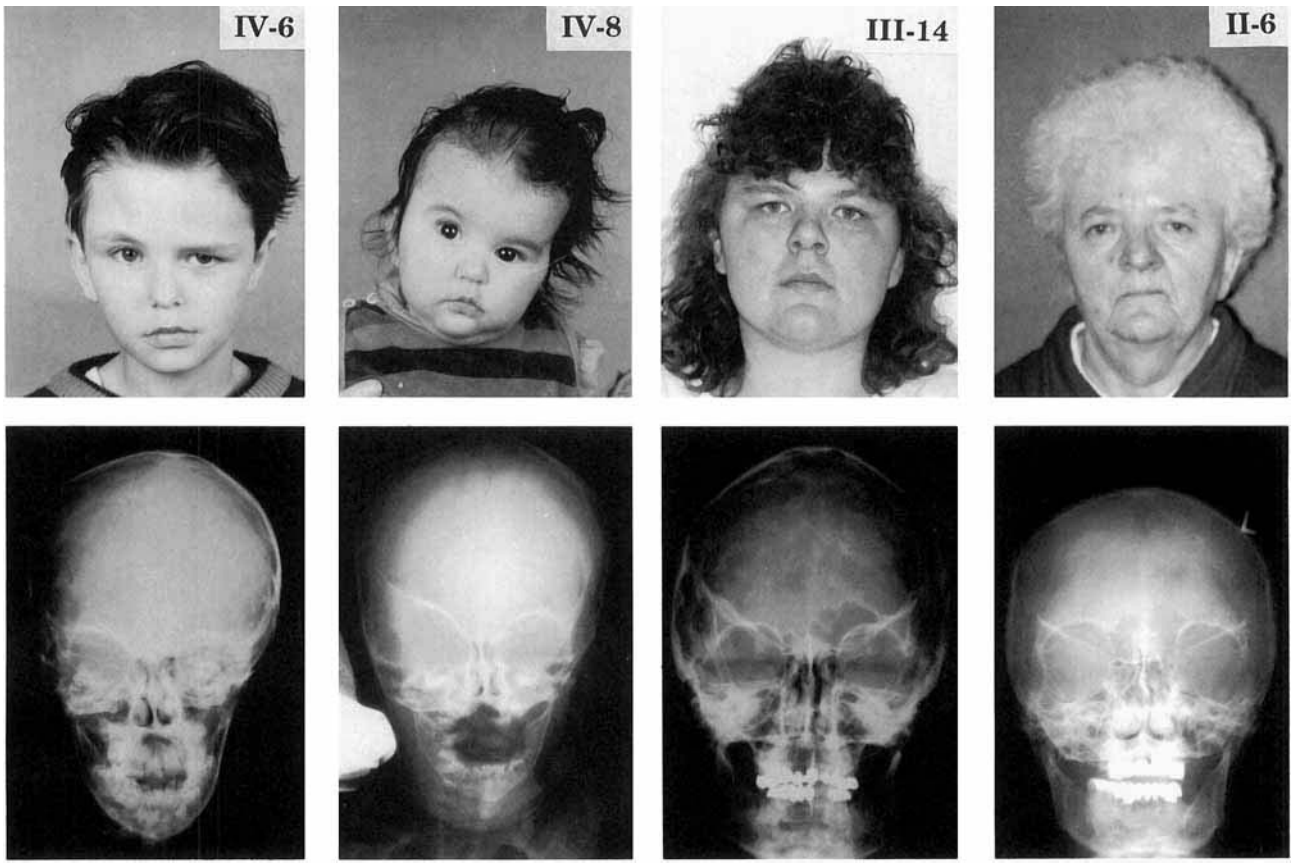

Fig. 2. Facial appearence and a.p. radiological views of the propositi (unilateral coronal suture synostosis) and two selected relatives (bilateral coronal synostosis). The two propositi (IV-6, IV-8) show marked asymmetry of the face, with unilateral flattening of the forehead. These clinical findings are confirmed in the radiographic views. Individuals III-14 and II-6 have bilateral coronal synostosis and broad flattened face. In III-14 the radiograph demonstrates marked indirect signs of raised intracranial pressure (impressiones digitatae), and virtual abscent development of the right frontal sinus

He was referred to the craniofacial unit at age 7.5 years (Fig. 2). His length (124 cm, 25th–50th centile), weight (22.4 kg, 50th centile), and OFC (52 cm, 50th–75th centile) were normal. Physical examination showed a mild pectus excavatum, low frontal hair line, and a slight lumbar hyperlordosis. A mild valgus deformity of toes 1 and 2 of both feet and slight partial soft tissue syndactyly between the second and third toe was noted (Fig. 4). No anomalies of the hands were present. Radiographic findings of the skull demonstrated a right sided coronal synostosis (Fig. 2).

Pedigree. In the mother's family six other individuals, with craniosynostosis and other extracranial anomalies, are known (Fig. 1). Of the 19 relatives investigated personally, including the mother of IV-6 and IV-8, 6 had signs of premature coronal synostosis, 4 with brachycephaly (II-6, II-9, III-12, and III-14), and two with plagiocephaly (II-12 and III-15). Other findings included facial asymmetry (II-9, II-12, III-15), low set frontal hairline (II-6, II-9, II-12, III-12, III-14, III-15), hypertelorism (II-6, II-9, II-12, III-12, III-15), strabismus (II-12, III-15), ptosis (II-12, III-15), deviation of the nasal septum (II-6, II-12, III-15), apparently low set ears (II-6, II-9, II-12, III-12, III-14, III-15), brachydactyly of 4th and 5th finger of the right hand (III-14), partial cutaneous syndactyly of 3rd and 4th finger of the left hand (III-12), partial cutaneous syndactyly of toes 2 and 3 of both feet (III-15), and hallux valgus (II-9, II-12). All affected members were of normal intelligence and height. Selected photographs of affected individuals are presented in Figs. 2–4. Manifestations of affected individuals are summarized in Table I.

Radiological studies of the skull in two relatives demonstrated a bilateral coronal synostosis (II-6 and III-14), confirming the clinical findings (Fig. 2). Roentgenograms of the hands and feet were available only on individual II-6 at age 58 years. No abnormalities were found (Fig. 5).

Linkage Results

Two point lod scores for markers D7S507 and D7S664 are shown in Table II. Assuming 100% penetrance a 3-point analysis provides exclusion of a 20 cM region including these markers (Fig. 6). The excluded region is reduced to 12 cM assuming a penetrance of

Fig. 3. Photographs of affected family members II-12, III-15, II-9 and III-12. Note the facial asymmetry and low hair line, apparently low-set ears, and ptosis of II-12 and III-15 (strabismus has been surgically corrected in both individuals). II-9 and III-12 demonstrate brachycephaly, apparently low-set ears, and a low hairline. There is no evidence of midfacial hypoplasia in any of these individuals. A beaked nose, often described in Saethre-Chotzen syndrome, is also not present.

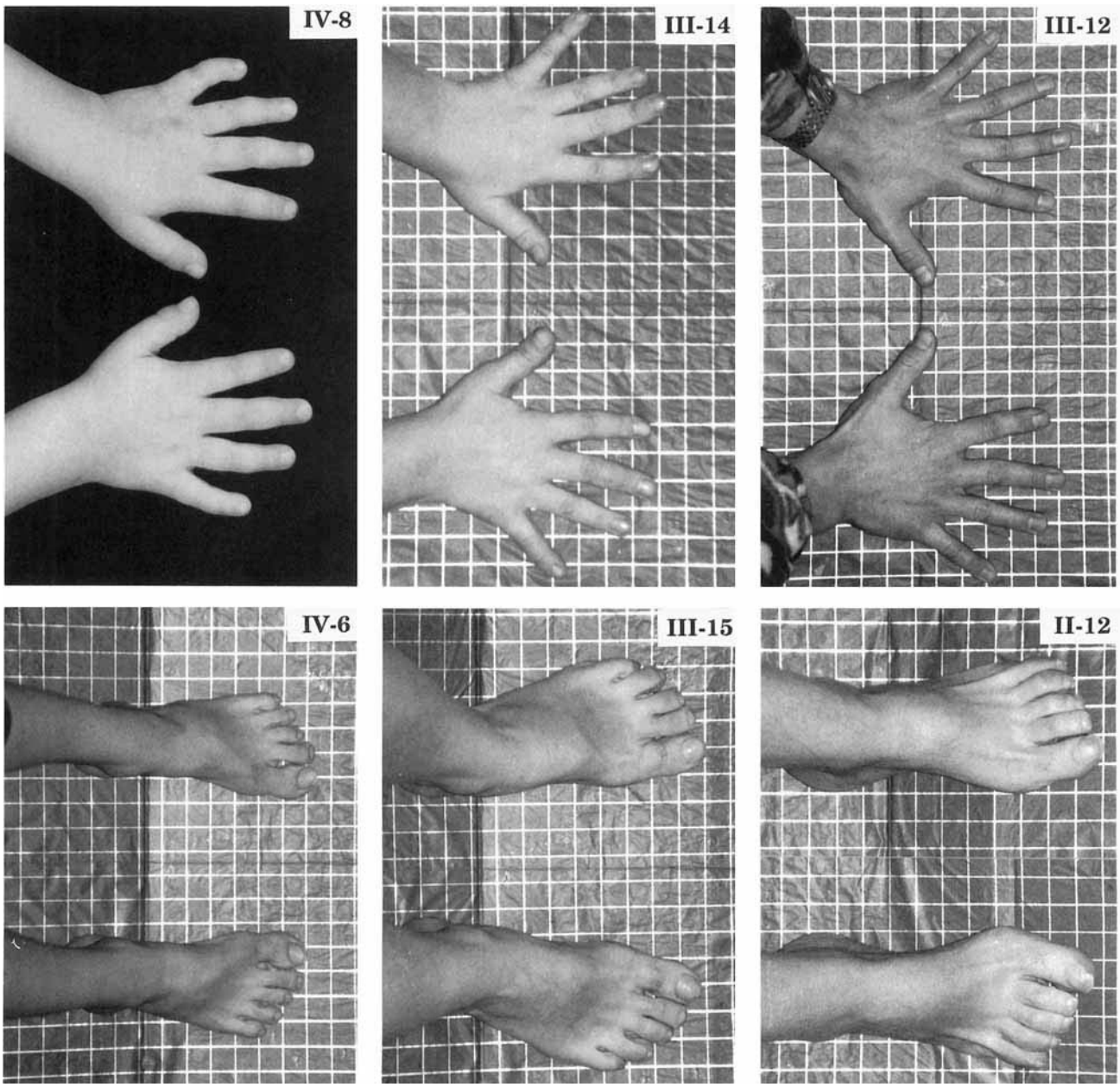

Fig. 4. Photographs of hands and feet from selected individuals showing mild abnormalities of the distal limbs. Note clinodactyly 5 of the left hand in IV-8, brachydactyly 4 and 5 of the right hand in III-14, partial syndactyly 3/4 in III-12, mild syndactyly of toes 2/3 (and hallux valgus) in IV-6, and syndactyly of toes 2/3 in III-15. Individual II-12 shows a mild hallux valgus deformity, which might be age-related.

80%. Thus, the gene locus in this family can be excluded from the Saethre-Chotzen region on 7p between markers D7S664 and D7S507 and also from the adjacent Saethre-Chotzen region between loci D7S488 and D7S654, which map 1 and 2 cM proximal to D7S507, respectively [Rose et al., 1994; Tsuji et al., 1995].

DISCUSSION

A number of large pedigrees with autosomal dominant craniosynostosis syndromes has been reported [Adès et al., 1994; Baraitser et al., 1980; Niemann-Seyde et al., 1991; Young and Harper, 1982]. Whilst Apert syndrome has a distinct and consistent phenotype characterized by symmetric cutaneous syndactyly with complete distal bony fusion and abnormalities of the shoulder girdle, Crouzon, Pfeiffer, Jackson-Weiss, and Saethre-Chotzen syndrome share many manifestations. Considerable variability of the phenotypes within and between families complicates the diagnosis and this has led to debate concerning the classification of these entities during the last decades [Cohen, 1986; Gorlin et al., 1990; Reardon and Winter, 1994].

TABLE I. Clinical Manifestations

	II-6	II-9	II-12	III-12	III-14	III-15	IV-6	IV-8
Age at examination (years)	58	57	52	31	30	30	7.5	0.6
Craniosynostosis	+	+	+	+	+	+	+	+
Plagiocephaly	–	–	+	–	–	+	+	+
Brachycephaly	+	+	–	+	+	–	–	–
Facial asymmetry	–	+	+	–	–	+	+	+
Low-set frontal hair line	+	+	+	+	+	+	+	+
Hypertelorism	+	+	+	+	–	+	+	+
Strabismus	–	–	+	–	–	+	–	+
Ptosis of the eyelids	–	–	+	–	–	+	–	–
Beaked nose	–	–	–	–	–	–	–	–
Deviation of nasal septum	+	–	+	–	–	+	+	+
Low-set ears	+	+	+	+	+	+	+	+
Prominent ear crus	–	–	–	–	–	–	–	–
Brachydactyly	–	–	–	–	+	–	–	–
Clinodactyly	–	–	–	–	–	–	–	+
Soft tissue syndactyly of fingers	–	–	–	+	–	–	–	–
Soft tissue syndactyly of toes	–	–	–	–	–	+	+	–
Broad great toes	–	–	–	–	–	–	–	–
Hallux valgus	–	+	+	–	–	–	+	–
Short stature	–	–	–	–	–	–	–	–
Hearing impairment	–	–	–	–	–	–	–	–
Mental retardation	–	–	–	–	–	–	–	–

Crouzon syndrome is characterized by proptosis and midface hypoplasia in almost every case, conditions which are not present in the pedigree described in this report.

Pfeiffer syndrome is similar to Apert syndrome, although less severe in its expression and is characterized by craniosynostosis, broad short thumbs, broad great toes, and partial soft tissue syndactyly of the hands. Broad short thumbs together with broad great toes, typical of Pfeiffer syndrome, were absent in all affected members of the family described and the diagnosis Pfeiffer syndrome was dismissed.

Jackson-Weiss syndrome is characterized by craniosynostosis, midface hypoplasia, and abnormalities of the feet. Marked variability of expression is well documented as for example in the large Amish kindred originally described by Jackson, in which the entire spectrum of dominantly inherited craniofacial dysostoses and acrocephalosyndactylies (except for Apert syndrome) was observed [Jackson et al., 1976]. The lack of midface hypoplasia and typical foot anomalies in the family under discussion make the diagnosis of Jackson-Weiss syndrome unlikely.

Characteristics of Saethre-Chotzen syndrome are craniosynostosis, low frontal hairline, facial asymmetry, ptosis, strabismus, deviated nasal septum, brachydactyly, partial cutaneous syndactyly, especially of the second and third fingers and various skeletal anomalies [Cohen, 1986; Gorlin et al., 1990; Reardon and Winter, 1994]. Craniosynostosis, described as a facultative rather than obligatory anomaly in Saethre-Chotzen syndrome, and low frontal hairline were observed in all affected relatives of the family. Four individuals had unilateral and another four bilateral coronal synostosis. Other findings pointing to Saethre-Chotzen syndrome were observed in some relatives: facial asymmetry (5/8), deviated nasal septum (5/8), strabismus (3/8), ptosis (2/8), partial cutaneous syndactyly of fingers (1/8) and toes (2/8), clinodactyly 5 (1/8), and brachydactyly (1/8).

Variable expression of Saethre-Chotzen syndrome has been documented and is also observed in the family described as evidenced by the presence of some of the typical traits in the eight affected members. Combining all aspects of the clinical findings the diagnosis of Saethre-Chotzen syndrome seems to be the most plausible.

Saethre-Chotzen syndrome was localized to 7p22-p15 by linkage analysis [Brueton et al., 1992] and by the identification of patients with apparently balanced

TABLE II. Pairwise Lod Scores Between Craniosynostosis Syndrome in the Family and Markers D7S507 and D7S664 Under Assumption of 100 and 80% Penetrance of the Disease

		Lod score at theta						
Marker	Penetrance	0.00	0.01	0.05	0.1	0.2	0.3	0.4
D7S507	1	$-\infty$	−5.44	−2.73	−1.64	−0.69	−0.26	−0.06
D7S507	0.8	−5.48	−2.58	−1.63	−1.09	−0.49	−0.19	−0.04
D7S664	1	$-\infty$	−4.21	−2.16	−1.33	−0.58	−0.23	−0.05
D7S664	0.8	−4.95	−3.09	−1.72	−1.09	−0.49	−0.19	−0.05

Fig. 5. Roentgenograms of the hands and feet of individual II-6.

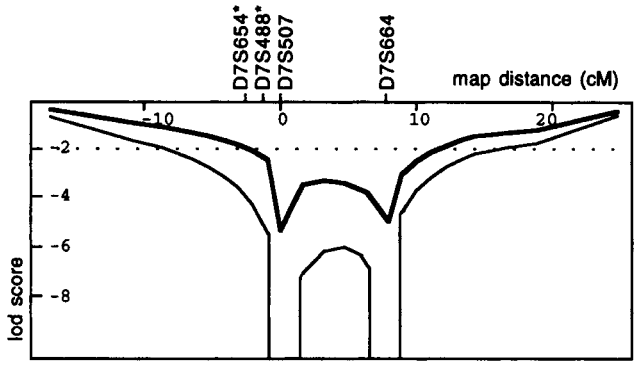

Fig. 6. Three point analysis of the craniosynostosis syndrome in the family and markers D7S507 and D7S664 from the Saethre-Chotzen syndrome candidate region. The location map indicates lod scores for the craniosynostosis syndrome in the marker map. D7S507 is arbitrarily placed at 0 cM, asterisk at markers D7S654 and D7S488 indicates that these markers were not included in the linkage analysis. Three point analysis was performed assuming a penetrance of 100% (thin line) and 80% (thick line). Note that the lod score is ≤ -2 (indicated by dotted line) in a 20 cM interval (100% penetrance) or 12 cM interval (80% penetrance) including the markers analysed and the markers D7S654 and D7S488 as well.

translocations [Reardon et al., 1993; Reid et al., 1993; Tsuji et al., 1994]. Further linkage analysis and physical mapping of translocation breakpoints have refined the localization of the Saethre-Chotzen gene(s) on 7p, and led to the definition of 2 adjacent candidate regions. One region maps between D7S664 and D7S507 and was identified by linkage analysis and a submicroscopic deletion in a translocation patient [Lewanda et al., 1994]. The second Saethre-Chotzen gene region was mapped more proximally by multipoint linkage analysis between D7S493 and D7S516 [van Herwerden et al., 1994]. This region was further narrowed to a 1 cM interval between D7S488 and D7S654 by determination of translocation breakpoints in two patients [Rose et al., 1994; Tsuji et al., 1995]. D7S488, which is the distal boundary of this region, shows a 1% recombination frequency with locus D7S507, which delineates the proximal boundary from the first Saethre-Chotzen region. Genetic heterogeneity on 7p, two independent genes with interacting products on 7p, or yet undetected complex rearrangements within the translocation regions have been discussed as explanations for these findings [Lewanda et al., 1994].

The craniosynostosis syndrome in this family was excluded from the two adjacent Saethre-Chotzen candidate regions on 7p, providing evidence for a Saethre-Chotzen syndrome locus different from those on 7p. This would provide a further example of locus heterogeneity in craniosynostosis syndromes, as shown in Pfeiffer syndrome with mutations in FGFR1 and FGFR2, Jackson-Weiss syndrome with mutations in FGFR2 and another as yet unidentified gene, and Crouzon syndrome with mutations in FGFR2 and FGFR3 [Cohen, 1995; Hollway et al., 1995; Jabs et al., 1994; Meyers et al., 1995; Muenke, 1995; Muenke et al., 1994; Reardon et al., 1994; Schell et al., 1995].

The point mutations of the fibroblast growth factor receptors detected in Pfeiffer, Crouzon, Apert, and Jackson-Weiss syndrome might act as "gain of function" mutations or dominant negative mutations. There is no evidence that haploinsufficiency of these genes may play a role in these syndromes. In contrast, the frequent finding of chromosome rearrangements in 7p21 in Saethre-Chotzen syndrome suggests that haploinsufficiency is a causative mechanism, as already demonstrated in the Greig cephalopolydactyly syndrome [Vortkamp et al., 1991]. Whether the Saethre-Chotzen phenotype in our family is allelic to other cran-

iosynostosis syndromes and whether haploinsufficiency or other types of mutations are causative remains to be seen. Further linkage studies of candidate genes such as FGFR1, 2, and 3, and MSX2 [Jabs et al., 1993] are in progress.

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